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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,353	06/08/2007	Jay Lal Mehta	056291-5246	8786
9629	7590	04/30/2008	EXAMINER	
MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004				BETTON, TIMOTHY E
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,353	MEHTA, JAY LAL	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 15 February 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 19-26 is/are pending in the application.

4a) Of the above claim(s) 20-26 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 19 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date See Continuation Sheet.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

Continuation of Attachment(s) 3. Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/15/2008 and 6/08/2007, 8 sheets.

DETAILED ACTION

Election of Species

Applicant's election without traverse in the reply filed on 15 February 2008 is acknowledged.

In response to the Elections/Restrictions requirement set forth beginning at page 2 of the November 16, 2007 Paper, Applicant hereby elects the invention of Group III, claims 19- 26, "drawn to various method procedures drawn to the administration of candesartan or a pharmaceutically acceptable salt thereof and rosuvastatin or a pharmaceutically acceptable salt thereof." In accordance with this election, non-elected claims 12-18 have been newly cancelled (claims 1-11 having been previously cancelled) without prejudice to Applicant's right to prosecute the subject matter thereof in one or more divisional applications. Although this election has been made without traverse, Applicant does not thereby acknowledge or otherwise imply its agreement with the Examiner's characterization of the teaching and/or relevance of the Otake et al. reference.

Claims 20-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 15 February 2008. Claim 19 is pending for further prosecution.

Beginning at page 4 of the November 16, 2007 Restriction Requirement, specifically the paragraph bridging pages 4 and 5, it is stated that "within the method species (claims 19- 26), applicant must elect either (1) a method of preventing or treating atherosclerosis, (2) a method of preventing cardiovascular events, (3) a method of

preventing or treating an inflammatory disease or condition, (4) a method of inhibiting expression of (i) CD40 or (ii) metalloproteinases (MMPs) or (iii) LOX-1, or (5) a method of treating atherosclerosis" (emphasis added), in response to this requirement for an election "within the method species" of claims 19-26, Applicant elects the first-stated species, "(1) a method of preventing or treating atherosclerosis," which is claim 19. In accordance with this election of species, claims 20-26 have been designated as withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating atherosclerosis, does not reasonably provide enablement for preventing atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

- 1) the quantity of experimentation necessary
- 2) the amount of direction or guidance provided
- 3) the presence or absence of working examples
- 4) the nature of the invention
- 5) the state of the art
- 6) the relative skill of those in the art
- 7) the predictability of the art and
- 8) the breadth of the claims

The prevention of atherosclerosis is disclosed in instant claim 9, however the amount of direction and guidance provided is deficient as far as adequately elucidating and distinguishing methods of treatment in comparison to the claim limitation of prevention. Specifically, applicants' attention is directed to the Materials and Methods disclosure (pages 7-11). An array of embodiments drawn to working models and experimentation are represented. The inventive objective drawn to methods of prevention are not suggested nor supported in any embodiments drawn to results.

Principally, the distinction between prevention and reduction is disclosed in the instant specification (page 3, 3rd full paragraph, last line). Accordingly, in the results portion of the experimentation (page 10 and 11), disclosures drawn to reduction and inhibition are present. However, embodiments or models adequately and substantially supporting preventive results are absent. Inhibition and reduction of expression as disclosed on page 3 of the specification has not been defined as prevention in the

specification. Nor is there guidance to lead the one of relative skill in the art that prevention has been achieved in any of the examples as disclosed in pages 7 -11).

Furthermore, unpredictability is high due to the lack of enabling embodiments drawn to cumulative data and/or comparative results. Terms disclosed within the results are suggestive a method of treatment. Even in the alternative, there is the absence of a clearly defined target population who have manifested with such disease states in need of such prevention. In other words, prevention is not reduction or inhibition. This is the central issue in the lack of scope of enablement for this current invention. Applicants have made this distinction as disclosed above (page 3). Additionally, applicants do not suggest or describe by prevention is meant *reduction and/or inhibition*.

The explanation above goes in accordance to the limitations in instant claim 9 drawn to the pharmaceutically acceptable salts of each bioactive agent thereof. The specification is silent upon any disclosure drawn to a method of prevention of atherosclerosis by administration of the pharmaceutically acceptable salts of candesartan and rosuvastatin.

Greenland et al. discloses that [m]ore than 40 years ago, a model that expressed then-prevailing concepts about atherogenesis¹ proposed that atherosclerosis begins relatively early in life (ages 10–20 years) with deposition of the fatty streak, progresses (ages 20–30 years) to the fibrous plaque, and further advances from ages 30–50 years by the action of traditional risk factors such as cigarette smoking, unfavourable blood lipid and blood pressure levels, overweight and insulin resistance (or glucose intolerance related factors) and eventually results in occlusive plaques and clinical manifestations of the atherosclerotic diseases from approximately age 50

onward. In this issue of the *International Journal of Epidemiology*, Beaglehole and Magnus² remind us that 'traditional' risk factors explain perhaps as much as 85% or more of the world's experience with atherosclerosis. **They state that research on further refinements of this model cannot add much to epidemiological knowledge of this disease, and they argue that more energy should be expended in lowering the prevalence of tobacco use, unfavourable cholesterol levels, dyslipidaemia, physical inactivity, and the obesity/insulin resistance syndrome** (Commentary: Lifelong prevention of atherosclerosis: the critical importance of major risk factor exposures, International Journal of Epidemiology, 2002; 31: 1129-1134), printed pages 1-10, especially page 1).

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Qin et al. (Effects of the combination of an angiotensin II antagonist with an HMG-CoA reductase inhibitor in experimental diabetes, (Kidney International (2003), 64, 565-571, printed pages 1 and 2, especially page 1 (please see abstract) in view of Leyland-Jones (USPGPUB 20030053950 A1) and Robl (USPN 6,620,821 B2) .

Essentially, Qin et al. teach the effects of the an angiotensin II antagonist combination of with an HMG-CoA reductase inhibitor (page 1, abstract).

An angiotensin II antagonist is the classification of bioactive agents which include candesartan and rosuvastatin is classified as an HMG-CoA reductase inhibitor.

Qin et al, however, does not teach the combination of these bioactive agents for atherosclerosis.

However, Leyland-Jones The invention relates to the individualization of therapy on the basis of a phenotypic profile of an individual. More specifically, the present invention relates to the use of metabolic phenotyping for the individualization of treatment with hyperlipidemia agents.

Leyland-Jones teaches several embodiments disclosing atherosclerosis and other diseases involving lipoprotein metabolism [0023]; [0104].

In response, paragraph 181 discloses rosuvastatin (Crestor) as a drug of choice for congestive heart disease of which atherosclerosis is indicated as a contributing and associative disease state.

Leyland-Jones does not teach candesartan for the treatment and/or prevention of atherosclerosis.

However, Robl does teach candesartan as a compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis [...] and pharmaceutically acceptable salts thereof [...] (abstract only).

Specifically, Robl is replete with embodiments drawn to atherosclerosis. Particularly, candesartan is indicated as suitable for use (column 37, line 19).

Furthermore, *in re Kerkhoven* cite: It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Thus, it would have been *prima facie* obvious to one of skill at the time of invention to at once recognize with an expectation of success the incorporating together of Qin et al. based on the motivation of Leyland-Jones and Robl alternatively or in combination.

The Qin et al. reference teaches the inventive objective of the claimed invention which is the concomitant therapy of candesartan with rosuvastatin. The deficiency of Qin et al. is resolved by the Leyland-Jones reference and the Robl reference, both separately and in conjunction with each other. The two secondary references teach motivation to treat atherosclerosis based on well-established protocols in their treatment of atherosclerotic conditions. Combinations of these agents are clearly defined and described in the above references indicated specifically for the treatment of atherosclerosis. Both agents are well-known in the art to treat atherosclerosis and all disease states associated.

The differences in any of the references, separately or in combination in view of the current invention is drawn to Qin et al. who indicates said combination treatment for diabetes. However, this difference in an indicated disease state is not further limiting based on well-known and established knowledge of the relatedness of certain disease states, i.e., atherosclerosis *inter alia* in regard to similar etiologies, susceptibilities and adverse events.

The objective evidence which is obvious in the current application is the claimed invention of an angiotensin-receptor blocker and a HMG-CoA inhibitor in concomitant/combination therapy. The necessity to combine agents in dual or poly-therapy is art-known for disease states such as hypertension, dyslipidemia, diabetic disorders, etc.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB

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